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Incentivizing Antibiotic Research and Development

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Abstract

Antibiotic Resistance is an international threat, killing thousands and infecting millions. Although certain populations may be at an increased risk for infections, anyone can find themselves compromised with a multi-drug resistant infection. Treatments are becoming more complicated as the bacteria becomes more elusive. Cures are becoming less certain, and the future antibiotic arsenal is looking thin. Although there are many talented scientists and capable drug development entities, the funding and returns on investment are not sufficient to entice antibiotic research and development.

This paper explores the current situation regarding antibiotic resistance and its casualties, as well as the mechanisms being employed to overcome the increase in resistance, and decrease in antibiotic effectiveness. Through analysis of antibiotic research, development, and regulation, this paper adds to the discussion by filling in the current gaps regarding the procurement of sustainable funding via an insurance model framework. By incentivizing the pharmaceutical industry to invest in antibiotic research, and by guaranteeing returns on investment, a global solution to the current antibiotic resistance problem can be contained.

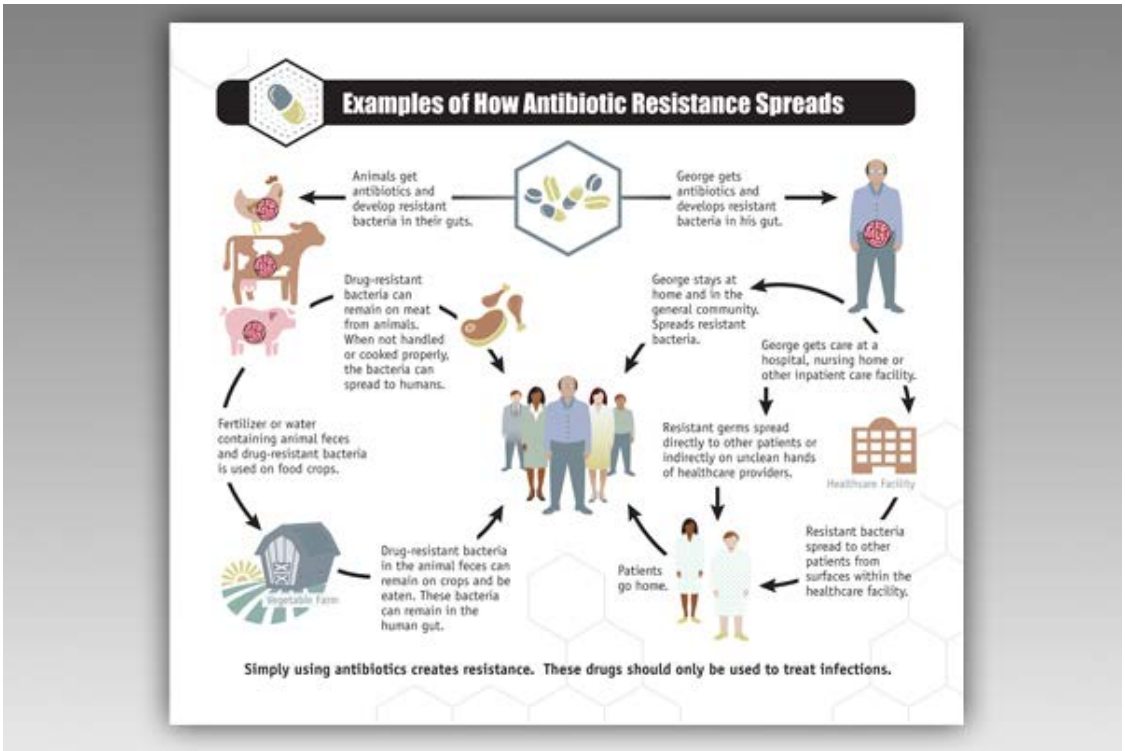
Introduction

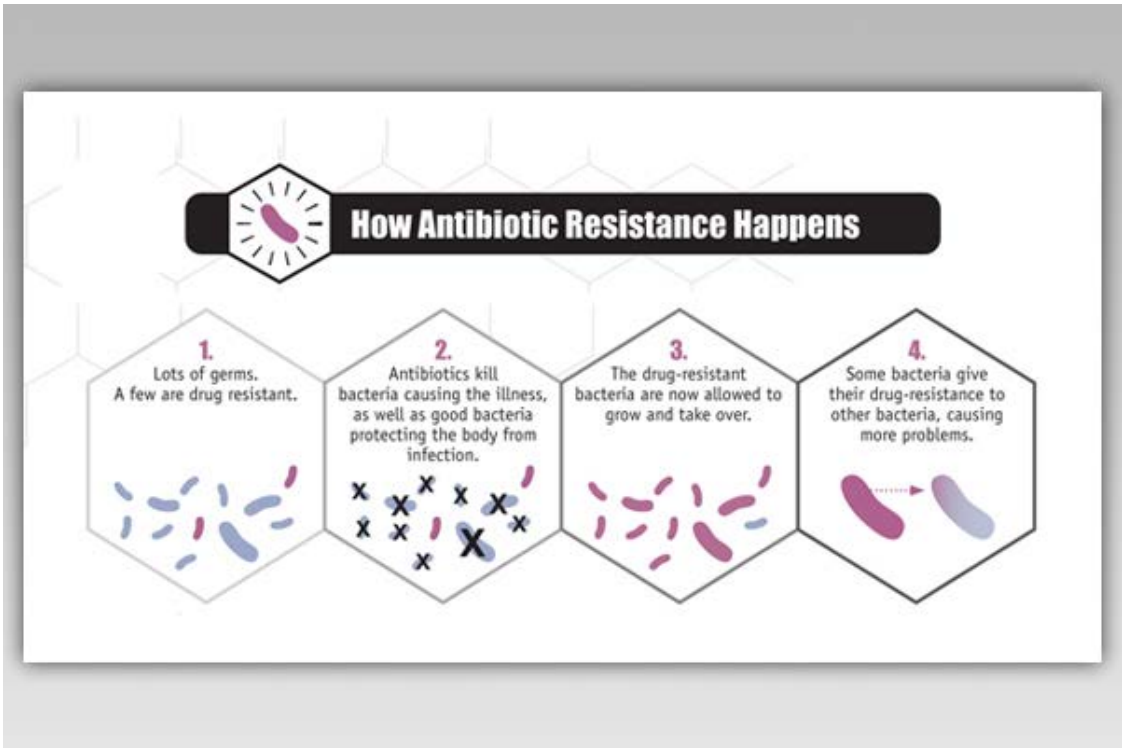
We are on the dawn of an international crisis. Infections are getting harder to treat, treatments are becoming more frequent, more expensive, and more people are dying.[1,2] Multi-drug resistant organisms (MDRO) are being found all over the world.[3] Many fear that infection treatment may return to a pre-antibiotic era, or a "post-antibiotic era," a time when tuberculosis, for example, was a death sentence. When the only prescription available was fresh air.[4,5,6] According to a BBC report, infections due to MDRO are estimated to rise more than tenfold, kill more than cancer currently does by 2050, and cost more than $100 trillion. Reporters believe these figures are an underestimate.[7] To make matters worse, there are not enough antibiotics being developed to satisfy the current and future needs.[8] The reasons for the lack of antibiotic drug development include difficulty developing novel drug classes, high costs of drug research and development, a challenging clinical trial drug approval process, and low to negative returns on investment.[5,9,10]

Methods

A preliminary literature search was done using PubMed. Articles that dealt with "antibiotic resistance," "antibiotic research and development," and "international policy and antibiotics" were included. President Barack Obama's Executive Order to Combat Antibiotic Resistance was analyzed, as well as the recommendations made by the President's expert advisors regarding antibiotic resistance. Follow-up questions were posed to experts in the field of antibiotic development, and their suggestions were investigated.

Findings





Antibiotic resistance emerges, even with appropriate antibiotic use, due to selection pressures that favor heartier, more clever, bacteria (figure 1, 2).[11]
http://www.cdc.gov/media/dpk/2013/dpk-untreatable.html

Misuse of antibiotics is also common.[12] In many countries antibiotics are readily accessible without a prescription.[13] Compound this with the fact that many patients seek antibiotics for non-bacterial infections, unaware antibiotics will not treat a viral infection such as a cold or flu.[14] Inappropriate antibiotic use extends beyond humans. Antibiotics are used, among other reasons, to promote growth in livestock in the United States and abroad.[15] Such use has been banned in the European Union.[16] However, even when used under the supervision of a veterinarian, there may be unintended residual consequences, and subsequent transmission of antibiotics to the consumer.[17]

Furthermore, there are not enough antibiotics to keep up with the growing bacterial resistance. Antibiotic Research and Development (R&D) is challenging.[10,18] Despite this, new classes of antibiotics are needed, and the current antibiotic pipeline is "thin."[18,19] Over the past eight decades, since the inception of antibiotics, there has not been sufficient antibiotic advancement to support our cavalier attitude toward infectious disease (table 1).

Table 1: Timeline of the discovery and introduction of antibiotics

Antibiotic class; example	Year of discovery	Year of introduction	Year resistance observed	Mechanism of action	Activity or target species
Sulfadrugs; prontosil	1932	1936	1942	Inhibition of dihydropteroate synthetase	Gram-positive bacteria
β-lactams; penicillin	1928	1938	1945	Inhibition of cell wall biosynthesis	Broad-spectrum activity
Aminoglycosides; streptomycin	1943	1946	1946	Binding of 30S ribosomal subunit	Broad-spectrum activity
Chloramphenicols; chloramphenicol	1946	1948	1950	Binding of 50S ribosomal subunit	Broad-spectrum activity
Macrolides; erythromycin	1948	1951	1955	Binding of 50S ribosomal subunit	Broad-spectrum activity

Tetracyclines; chlortetracycline	1944	1952	1950	Binding of 30S ribosomal subunit	Broad-spectrum activity
Rifamycins; rifampicin	1957	1958	1962	Binding of RNA polymerase β-subunit	Gram-positive bacteria
Glycopeptides; vancomycin	1953	1958	1960	Inhibition of cell wall biosynthesis	Gram-positive bacteria
Quinolones; ciprofloxacin	1961	1968	1968	Inhibition of DNA synthesis	Broad-spectrum activity
Streptogramins; streptogramin B	1963	1998	1964	Binding of 50S ribosomal subunit	Gram-positive bacteria
Oxazolidinones; linezolid	1955	2000	2001	Binding of 50S ribosomal subunit	Gram-positive bacteria
Lipopetides; daptomycin	1986	2003	1987	Depolarization of cell membrane	Gram-positive bacteria
Fidaxomicin (targeting Clostridium difficile)	1948	2011	1977	Inhibition of RNA polymerase	Gram-positive bacteria
Diarylquinolines; bedaquiline	1997	2012	2006	Inhibition of F1FO-ATPase	Narrow-spectrum activity (Mycobacterium tuberculosis)

Nature Reviews Drug Discovery 12, 371-387 (2013), www.nature.com.nrd/journal/v12/n5/fig_tab/nrd3975_T1.html

Perhaps in response to the current antibiotic need, the field of antibiotic research, development, regulations, and policy-making is an exciting, interdisciplinary, charming, solution-focused, and widely innovative space.[19,20]

Recently there has been collaboration to find solutions to the combined lack of innovation and increasing threats due to antimicrobial resistance. Due to the work of many skilled and passionate leaders in the antimicrobial resistance specialty, there has been substantial progress made through international dialogue. Bacterial diagnostics have seen recent attention, and are the focus of the 2014 Longitudinal Prize.[21] Antimicrobial Stewardship is flourishing, and has seen an encouraging push from the Executive Branch with President Obama's recent Executive Order to Combat Antibiotic-Resistance on September 18, 2014. In this report, President Obama requires antimicrobial stewardship initiatives across various health care settings, including long-term care facilities.[22] President Obama based the executive order on a report, Combating Antibiotic Resistance, developed by an expert panel with the President's Council of Advisors on Science and Technology (PCAST).[23]

The United States federal government has recognized the threat of antimicrobial resistance (table 2), and has responded in various ways.

Table 2: Resistant bacteria and representative infections, alternatives

Current and Emerging Resistant Bacteria	Type	Representative Clinical Infections	Antibiotics Associated with Resistance	Treatment Options (as determined based on culture & sensitivity, local guidelines, clinical presentation)
Methicillin-resistant Staphylococcus aureus (MRSA)	gram (+) cocci	skin/soft tissue infections, UTI, bacteremia, toxic shock syndrome, pneumonia, osteomyelitis, endocarditis, meningitis; assoc. with IV catheters	beta-lactam antibiotics (eg., oxacillin, penicillin, nafcillin, amoxicillin, and most cepholosporins) erythromycin	vancomycin alternatives: linezolid; clindamycin (confirm with D-test); daptomycin; TMP-SMX; quinupristine-dalfopristin
Vancomycin inter-mediate and resistant Staphylococcus aureus (VISA/hVISA/VRSA)	gram (+) cocci	skin/soft tissue infections, UTI, bacteremia, toxic shock syndrome, pneumonia, osteomyelitis, endocarditis, meningitis	vancomycin; beta-lactam antibiotics (eg., oxacillin, penicillin, nafcillin, amoxicillin, and most cepholosporins) erythromycin	linezolid; clindamycin; daptomycin; TMP-SMX; quinupristine-dalfopristin

Community-acquired methicillin-resistant Staphylococcus aureus (cMRSA)	gram (+) cocci	necrotizing pneumonia; skin infections, boils, abcesses (seen in IV drug abusers, athletes who share equipment, day care centers, military personnel; prisons); drainage of abscess is primary treatment; treat with antibiotic only if needed[2]	beta-lactam antibiotics (eg., oxacillin, penicillin, amoxicillin, and most cepholosporins, erythromycin	doxycycline or minocycline; clindamycin (confirm with D-test); linezolid; TMP-SMX
Streptococcus pneumoniae (multi-drug resistant)	gram (+) diplo-coccus	pneumonia, otitis media, sinusitis, bronchitis, bacteremia, peritonitis, cellulitis, meningitis, arthritis	multi-drug resistance; penicillin G, cephalosporins, TMP-SMX, erythromycin, doxycycline	for multi-drug resistance consider: vancomycin +/- rifampin; fluoroquinolone (gemifloxacin, moxifloxacin), levofloxacin) alternatives: linezolid; clindamycin ; imipenem/cilastatin
Escherichia coli (E. Coli) - CTX-M extended spectrum beta-lactamases (ESBL)	gram (-) rod	UTIs	Oral cephalosporins, TMP/SMX, fluoroquinolones	Fosfomycin , nitrofurantoin, ertapenem, doripenem, imipenem/cilastatin
Enterococcus faecium (E. faecium) vancomycin resistant enterococci (VRE)	gram (+) cocci	meningitis, UTI, bacteremia (central venous catheter-related), endocarditis	vancomycin; streptomycin; gentamicin; penicillin; ampicillin	linezolid; quinupristine-dalfopristin; daptomycin, fosfomycin (for UTI)

Pseudomonas aeruginosa (multidrug resistant strains)	gram (-) rod	UTIs, pneumonias, skin and soft-tissue infections, endocarditis, meningitis	imipenem/cila-statin, mero-penem, non-antipseudo-monal penicillins, oral cephalosporins,	colistin, polymyxin B (for multidrug resistant strains)
Klebsiella pneumoniae -extended spectrum beta-lactamases (ESBL)	gram (-) rod	pneumonias, UTIs, upper respiratory tract infections, surgical wound infections	2nd, 3rd generation cephalosporins; aztreonam; carbapenems	imipenem; meropenem; colistin
multi-drug resistant Mycobacterium tuberculosis (MDR-TB)	acid-fast	tuberculosis (lung infection)	isoniazid; rifampin; possibly streptomycin	multiple agents required for treatment: aminoglycoside (amikacin or kanamycin) or polypeptide antibiotic (capreomycin) + antimycobacterials (pyrazinamide + ethambutol) + fluorquinolone (moxifloxacin) + rifabutin; other agents may need to be substituted based on drug availability
Acinetobacter baumanii	gram (-) rod	immunocompromised patients: pneumonia (commonly ventilator-associated), UTI, septicemia, central venous catheter-related infections, traumatic wound infections	imipenem; meropenem; antipseudomonal agents, fluoroquinolones, carbapenems	ampicillin-sulbactam; colistin

Staphylococcus epidermidis (methicillin resistant)	gram (+)	bacteremia, catheter, implant, and prostheses-related infection (biofilm formations), endocarditis	penicillin, amoxicillin	vancomycin if infected implant, surgical removal or replacement may be required; vancomycin +/- (rifampin + gentamicin) alternative regimens if vancomycin resistant: daptomycin, linezolid

http://www.drugs.com/article/antibiotic-resistance.html#s2

The Biomedical Advanced Research and Development Authority (BARDA), within the Office of the Assistant Secretary for Preparedness and Response, in the Department of Health and Human Services, established a Broad Spectrum Antimicrobials (BSA) program in April 2010 to address the growing rise of antimicrobial resistance. The National Institute of Allergy and Infectious Diseases (NIAID) has held groundbreaking meetings and contributed funds to antibiotic research. The Centers for Disease Control and Prevention (CDC) has also invested in the cause to contain antibiotic resistance. There have been attempts from the Food and Drug Administration (FDA) to streamline the antibiotic approval process. The FDA has held a series of talks to address the challenges facing the antibiotic approval process, most recently in December 2014. Results of the meetings have been mixed, but undeniably promising in their consideration of recent proposals, including widening the non-inferiority margin, considering a tiered clinical trial infrastructure, use of a sufficient historical-control in place of an active control in clinical trials, dual indication evaluation within one trial, the possibility of pathogen-focused labeling, and use of a pharmadynamic/pharmakokinetic, in vitro/in vivo, translational study in place of a second, randomized control trial normally needed for drug approval.[18,19,24,25] Overseas, the European Medicines Agency (EMA), the European Union's version of the FDA, has also contributed substantially to the efforts aimed to curb antibiotic resistance.[26] Everywhere from Mexico to Scotland seems to recognize the growing need for intervention.[27,28,29]

Additionally, a number of highly qualified and innovative groups, including international and public-private partnerships that unite academia, government, and industry, have come together over the issues of antibiotic resistance. The Wellcome Trust and the Bill and Melinda Gates Foundation have been major contributors in the effort to fund antibiotics research and development.[30] New Drugs for Bad Bugs (ND4BB) has been developed under the auspice of the Innovative Medicines Initiative (IMI), based in Europe. The Antibacterial Resistance Leadership Group (ARLG) has recently formed, and is providing grants to contribute to antibiotic development at smaller institutions.[31] There is also the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) and The Infectious Diseases Society of America (IDSA), which pay substantial attention to antibiotic resistance, and have united thought leaders across international borders. The Alliance for the Prudent Use of Antibiotics (APUA) is based in Boston, MA, at Tufts University, and boasts international efforts and a comprehensive newsletter.[32] There is also the International Society for Chemotherapy, Infection, and Cancer (ISC), which has several journals and workgroups that address the challenges of antibiotic resistance. Additionally, The World Health Organization (WHO) has developed surveillance software to monitor international resistance patterns.[33] Worth noting is the substantial investment made by some leadership and scientists within the pharmaceutical industry, when many chose to pull their research and development teams out of the antibiotics game. Astra Zeneca, Cubist, GlaxoSmithKline, F. Hoffman-la Roche, The Medicines Company, Astellas, and Pfizer have been involved in antibiotic development despite the challenges described henceforth.[34] Interestingly, Merck made a recent decision to acquire the pharmaceutical company Cubist, known mostly for its antibiotic Cubicin, for $8.4 billion.[35] It is possible Merck's decision will be rewarded, considering Cubist's very recent approval, on December 22, 2014, of combination drug Zerbaxa, to treat urinary tract and abdominal infections.[36]

Summary

Although it is clear that many efforts have been made to preserve the effectiveness of current antibiotics, and foster more antibiotic research and development, the challenge remains to create a financial solution. What remains to be seen is a new economic model that would ensure antibiotics research, development, and availability. Through the IMI's ND4BB platform, DRIVE-AB (Driving

reinvestment in R&D for antibiotics and advocating their responsible use) held its inaugural meeting in Geneva, Switzerland in October 2014. DRIVE-AB is an international group creating and testing new economic models that would enable self-sustaining antibiotic research. One can hope that an answer to self-sustaining antibiotics research will surface through the work of these thought leaders. The following proposal may be worth their consideration, as it lays the foundation for an unconventional economic model that would enable self-sustaining antibiotic research through a Central Body, a synthesized payer/financier/surveillance entity.[37] This model has been inspired, in part, by the revitalized framework developed by the global agricultural research partnership, CGIAR.[38]

Recommendations

The Central Body

Create a single, "Central Body," devoted to antibiotic resistance. This will allow overhead expenses to be reduced, so that both scientific and economic resources can be streamlined. Within this paper alone, at least five separate groups devoted to antibiotic resistance have been mentioned. While current efforts are admirable, and must continue, within one Central Body it will be possible to streamline intellectual efforts, and avoid the unknown simultaneous duplication of important work, making the best use of limited resources.

Create a single, "Central Fund," much like CGIAR has done.[38] It will become important to easily document the flow of funds, and reduce the duplication of costs encountered by running multiple, not fully synchronous antibiotic resistance entities.[30] It should be possible for anybody interested in donating money, or doing "a walk to benefit antibiotic resistance," to donate to antibiotic research. One should be able to donate money as easily to antibiotic research as they would cancer research. This would necessitate that this Central Body be a non-profit entity, attaining 501(c)(3) status. A model proposing a non-profit industry entity has been suggested.[39] However, it should not be necessary to restructure the current drug development body within the pharmaceutical industry. The pharmaceutical industry, is already so good at developing drugs, what needs to be done is to fund the work from a separate entity, the Central Body, while incentivizing the pharmaceutical industry--allowing them to profit on the product they create. The Central Body could always negotiate a percentage of the profits if it would like.

The Central Body should have a Public Relations (PR) department that can give a face to antibiotic resistance. That is, to "brand" antibiotic resistance. The goal of this would be to educate the general public about the serious nature of antibiotic resistance, and that a world without effective antibiotics is inevitable without intervention. It is important to bring a sense of value and appreciation to antibiotics. Without a profound shift in the current paradigm, antibiotics will continue to be taken for granted--and no one will want to pay what they are worth until it is too late to pay any amount for them.

International government involvement will be necessary, as mentioned in the PCAST Report to the President on Combating Antibiotic Resistance.[23] As far as the entities that pay for antibiotics, there are two models that seem possible in the United States. The following managed care/insurance models could be applied to the federal governments in nations whose federal governments pay for pharmaceuticals.

The first Managed Care Model would be to incorporate a single Pharmacy Benefit Manager (PBM) within the Central Body. This single PBM (a pharmacy benefit expert contracted on behalf of the Managed Care Organizations (MCOs), or insurance companies) would handle the antibiotic coverage of the entire population of the United States. This PBM could determine formulary management and protocols that fit regional resistance patterns, or let local antimicrobial stewardship entities determine proper pharmaceutical use. Such local to global considerations would be possible if everyone is linked via the Central Body. This could potentially be a way to look at antimicrobial stewardship from an epidemiological level. The data collected from this central PBM could be as robust as the Central Body would realistically like it to be, including diagnostic/morphologic/genetic data, if they would like to link diagnostics to billing codes. A lot of valuable resistance and prescribing data could be documented in a central database, and interpreted. This would be an answer to the PCAST request for effective surveillance and response.[23]

A second Managed Care Model would be to keep the current PBM/MCO structure intact, but appeal to them that the importance of paying more for antibiotics than the PBM/MCO may be used to is imperative. A good pharmacoeconomic evaluation of the new and different pharmaceuticals would be paramount. As much as the direct costs of antibiotic resistance is a public or federal concern, it should be of great concern to the MCOs who are paying for the medical complications due to antimicrobial resistance. Traditionally these two benefits, pharmacy vs. medical, have been siloed from one another, or viewed as separate entities. The pharmacy side

tries to keep their costs down without regard to the medical costs, and vice versa. Recently the "silo" paradigm has shifted. The pharmacy and medical benefit are merging, especially in regards to the rising cost of specialty pharmaceuticals.[40] Today, PBMs, including government plans, are paying for very expensive medicines, such as Sovaldi for Hepatitis C, because it is often curative, staving off more expensive procedures (i.e. liver transplants) and deleterious side effects of other treatment options.[41] Gilead, the makers of Sovaldi, have seen $8.55 billion in sales within the first nine months of its launch.[42] Sales such as those seen with Sovaldi make an important statement regarding the willingness of MCOs to pay more than they have traditionally for hard-to-treat-infections. To extrapolate to the antibiotic arena, it seems reasonable that PBMs would pay more for effective antibiotics, in the face of resistance, in order to avoid a week long hospital admission to treat a complicated Urinary Tract Infection (cUTI), or longer when the untreatable UTI causes the patient to become septic.

It is a fantastic climate to engage PBMs and MCOs in discussions about the possibility of paying more for future antibiotic prospects, and to possibly start negotiating payment contracts. It would behoove the pharmaceutical industry to hire pharmacoeconomists to appeal to these MCO entities to explain that although an antibiotic looks expensive, it will save money on the medical side. It would behoove the PBM and MCO, on the other hand, to have a specific antibiotic benefit management individual, or department. This entity should also be part of the antibiotic resistance discussion, and part of the Central Body. This conversation must be had on all sides.

The preceding applies directly to the outpatient setting. There are logistical benefit/reimbursement hurdles in the inpatient setting. Ultimately, however, these pharmaceuticals used in the inpatient setting will need to be paid for by either the PBM or MCO, depending on if they fall under the pharmacy or medical benefit, respectively. The biggest MCO happens to be The Centers for Medicare and Medicaid Services (CMS), a federal entity. The negotiations concerning the value-based reimbursement of novel antibiotics could be linked to appropriate antimicrobial stewardship practices, as many other CMS reimbursements are tied to performance indicators. It would be possible to negotiate a contracted price for these drugs so that hospitals could be incentivized, via reimbursement contracts, to have these inevitably expensive, novel drugs, to combat antibiotic resistance on their hospital formulary. This would help to avoid the seemingly inevitable market failure of better, necessarily more expensive antibiotics.

Each hospital should be engaged in antimicrobial stewardship at the local level. If these new pharmaceuticals are effective and are needed, and if the infectious disease representatives from the hospital are part of this Central Body, the adoption onto formulary of these novel drugs seems promising. It only makes sense to pay a little more up front to avoid very expensive hospital stays, instead of posing the additional risks of developing a hospital acquired bacterial pneumonia, or ventilator acquired bacterial pneumonia (HABP/VABP), that we may or may not be able to treat. Additionally, it would behoove medicare to cover home infusion, allowing our older populations in nursing homes to be covered for intravenous antibiotics without the need to be admitted to the hospital, where they are prone to subsequent infection and falls.

Create contracts through the Central Body to find and develop needed antibiotics, and let the private sector bid on them.[37] The Central Body could accept the offer it sees most suitable, and could provide a lump-sum dispersement, or installment payments, to the private sector. This would give the private sector reliable, predictable payments, and would incentivize antibiotic R&D. As would happen when a new building or mall must be built, the main contractor within the private sector could draft scientists or entities, such as academic institutions capable of performing pre-clinical or phase-I trials, within the Central Body. This would all be possible if the best minds in antibiotic drug R&D were organized within one central organization, such as the Central Body.

Next, Marketing must be considered.[10,43] The Marketing Department within the pharmaceutical company will evaluate the needs of the pharmaceutical market, and determine the fate of a drug (i.e. if a chemical entity will finish its development). If the Marketing Department of the pharmaceutical company is not part of The Central Body, they will not be aware of all of the new changes taking place in the landscape of antibiotic drug development. It is imperative to include Marketing in the Central Body. The Marketing department will develop relationships with the PBMs and MCOs to get these novel antibiotics paid for. Here, as in the MCO/PBM, there should be a team, or individual, devoted to antibiotics. The antibiotic marketplace will be a unique one, and will require a specific skill-set and ability to develop good relationships with the government, MCOs/PBMs.

The future is unclear, but one is wise to be hopeful. Solutions to the economic conundrum that belies the high expense, and low return on investment, can be found with cooperation. When the MCOs agree to pay more for antibiotics, understanding they will save resultant pharmacy and medical fees attributable to treatment failures, it will help incentivize the pharmaceutical industry to

invest in antibiotic R&D. When the hospital formulary committees agree to put better antimicrobial options on their formularies, because better outcomes result in shorter hospital stays (possibly even limiting a hospital stay to the Emergency Department), it will help incentivize the pharmaceutical industry to invest in antibiotic R&D. When the pharmaceutical industry does not have to lose money, and can potentially see returns on their investment, they will invest in antibiotic R&D. If this can happen, it will not be necessary to place our hope of cure in the fresh air, as was done before the advent of antibiotics.

The proposed solutions in this document address the need for a new economic model that enables sustainable antibiotic R&D. To my knowledge, these ideas have not been addressed by the many different thought leaders in the antibiotic resistance spectra, with the exception of recommending the need for a new, possibly insurance-based, economic model.

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